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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,650	WEINER ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,14-17,19,21-23,38 and 54-77* is/are pending in the application.

4a) Of the above claim(s) *38,64 and 75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,14-17,19,21-23,54-63,65-74,76 and 77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's claim amendments filed on 01/29/2009 have been entered. Applicant's response filed on 11/04/2009 to the requirement for Restriction/Election, necessitated by claim amendment and mailed on 05/05/2009, has been entered.

This application, 10/560,650, is a 371 of PCT/US04/18962 filed on 06/14/2004, which claims benefit of provisional application 60/478,205 filed on 06/13/2003 and claims benefit of provisional application 60/478,210 filed on 06/13/2003.

Election/Restrictions

Applicant's election with traverse of cytokine recited in claim 1 and IL-15 recited in newly added claim 77 in the reply filed on 11/04/2009 is acknowledged. The traversal is on the ground(s) that while each species is patentably distinct from the other species they are not linked as to form a single general inventive concept. Claim 77 refers to nucleic acid molecules that comprise nucleic acid sequences that encode a fusion protein which comprises an IgE signal peptide linked to a non- IgE protein. Thus, the nucleic acid molecules encode fusion proteins with the common feature of having both an IgE signal peptide and a non-IgE protein region.

This is not found persuasive because as stated on pages 4-5 of Election/Restrictions requirement mailed on 05/05/2009 the species listed in claims 1 and 77 are patentably distinct because they are different proteins encoded by different genes and have different biological functions. Furthermore, as stated on page 6 of Election/Restrictions requirement mailed on 05/05/2009, upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the

limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Claims 2-13, 18, 20, 24-37, and 39-53 are cancelled. Claims 1, 21-23, 61-63, 73, and 74 are amended. Claim 77 is newly added in the claim set filed on 01/29/2009. Claims 1, 14-17, 19, 21-23, 38, and 54-77 are pending

It is noted that as Applicant elected cytokine as the species recited in claim 1, claims 38, 64, and 75 are directed to non-elected species "enzymes or functional fragment thereof" recited in claim 1. Therefore, claims 38, 64, and 75 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1, 14-17, 19, 21-23, 54-63, 65-74, 76 and 77 are currently under examination to the extent of elected species, cytokine IL-15.

The requirement is still deemed proper and is therefore made FINAL.

Claim Objection

1. Previous objection of claims 1, 21, 22, 23, 55, 61-63, 73, and 74 for the informalities is ***withdrawn*** because the claims have been amended.

Claims 1 and 55 have been amended to recite "an IgE signal peptide".

Claims 22, 62, and 73 have been amended to recite "A recombinant vaccine".

Claims 21 and 22 have been amended to recite "a nucleic acid molecule of claim 1".

Claims 61 and 62 have been amended to recite "a nucleic acid molecule of claim 1"

Claims 23, 63, and 74 have been amended recite "a recombinant vaccine comprising a vaccinia virus vector".

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

2. Claims 66 and 77 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. *This rejection is necessitated by claim amendments filed on 01/29/2009.*

Claim 66 depends from claim 1 and recites the limitation "wherein the non-IgE protein is an immunomodulating protein". It is unclear "the non-IgE protein" recited in claim 66 is referring to "a non-IgE protein sequences" recited in lines 3-4 of claim 1 or referring to "a non-IgE protein sequences" recited in lines 6-7 of claim 1. In latter scenario, lines 7-8 of claim 1 have been amended to recite additional limitation "wherein the non-IgE protein is an immunomodulating protein".

Newly added claim 77 recites the limitation "wherein the immunomodulating protein is selected from the group consisting of wherein the non-IgE protein is an immunomodulating protein selected from the group consisting of ---". It is unclear what this limitation is intended to mean. As a relevant issue, Applicant's attention is directed to the claim interpretation stated in the 103 rejection documented in this office action.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of enablement

3. Claims 21-23, 54, 61-63, 65, 72-74, and 76 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising an isolated nucleic acid molecule, wherein the isolated nucleic acid molecule comprises a nucleic acid sequence consisting of a nucleic acid sequence that encodes a fusion protein that consists of either a non-IgE protein or an immuno-modulating protein sequence linked to an IgE signal peptide, **does not** reasonably provide enablement for (1) any pharmaceutical composition or (2) any DNA vaccine for generation of a protective immunity against the infection of a pathogen or against the development of a disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Applicant's arguments filed 01/29/2009 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 4-9 of the office action mailed on 07/29/2008.

For clarity and completeness of this office action, the rejection for the reasons of record advanced on pages 4-9 of the office action mailed on 07/29/2008 is reiterated below.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as

routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

It is noted that a vaccine is interpreted to be used for providing protective immunity. The claims are being examined to this end for the purpose of the instant rejection.

The nature of the invention is directed to a composition comprising an isolated nucleic acid molecule for generation of an immune response in a subject, wherein upon administration of the nucleic acid that expresses a fusion protein consisting of an IgE signal/secretory peptide fused to a non-IgE protein or fused to an immuno-modulating protein, an immune response in the subject is induced. The specification discloses that the composition is intended for pharmaceutical use as a recombinant DNA vaccine. The breadth of the claims reads on any pharmaceutical composition and any recombinant DNA vaccine, wherein the pharmaceutical composition is used as a recombinant DNA vaccine and comprises an isolated nucleic acid molecule for generation of *any* immune response, including protective immunity in a subject against infection of a pathogen, or against the development of a cancer or an autoimmune

disease, via administration of the nucleic acid that expresses a fusion protein consisting of an IgE signal/secretory peptide fused to a non-IgE protein or fused to an immuno-modulating protein.

The specification teaches IL-15 is a prototypic Th1 cytokine and an engineered IL-15 plasmid vaccine was constructed by removing the native IL-15 Kozak region, AUG's and UTRs, and the engineered IL-15 plasmid was provided with the coding sequence for IgE signal peptide. The engineered IL-15 was expressed at a level 30 to 50 times greater than that observed with a comparable wild type plasmid, and the immune response observed in mice co-immunized with engineered IgE signal-IL-15 and HIV-1 gag constructs were significantly greater than mice immunized with the HIV-1 gag construct alone (See Example 4, paragraphs [2004] and [213], and Figure 16, 2007/0041941, publication of instant application). This example demonstrates the effect of expression of a cytokine such as IL-15 in enhancing the immune response elicited by the expression of HIV-1 gag.

With regard to the effect of expression of an antigen other than gag protein of HIV-1 in eliciting an immune response in the art, Yang et al 2001 disclosed a DNA vaccine encoding the West Nile Virus (WNV) capsid protein (Cp) was constructed, and the *in vivo* immune responses generated in DNA vaccine-immunized mice, and antigen-specific humoral (i.e. antibody mediated) and cellular (i.e. T-cell mediated) immune responses were observed, including a potent induction of antigen-specific (i.e. WNVCp-specific) Th1 and cytotoxic T lymphocyte responses, and dramatic infiltration of $CD4^+$ and $CD8^+$ T cells and macrophages also was observed at the muscle injection site. These results support the potential utility of this method as a tool for developing immunization strategies for WNV and other emerging pathogens (See

abstract, Yang et al., Induction of potent Th1-type immune responses from a novel DNA vaccine for West Nile virus New York isolate (WNV-NY1999). *J Infect Dis.* 184(7):809-16, 2001).

However, it is noted that the specification and the art cited above do not provides enabling support regarding whether the immune response to HIV-1 gag protein or WNVCp protein can be long-lasting and effectively prevent the immunized subject from HIV or WNV infection. It is worth noting that the breadth of the claims reads on any DNA vaccine, for instance, a vaccine providing protective immunity against any pathogen infection, and a cancer vaccine providing protective immunity against processes of tumor development, and a vaccine providing protective immunity against any autoimmune disease. The specification does not provide any enabling support with regard to a vaccine providing protective immunity against any pathogen infection, a vaccine providing protective immunity against any cancer development, and a vaccine providing protective immunity against any autoimmune disease.

In the art, the effectiveness of DNA vaccination as an approach for generation of protective immunity against a pathogen is unpredictable in general. For instance, **Belakova et al.** discusses critical factors affecting effectiveness of a DNA vaccine. These factors include (1) efficacious expression of protein DNA vaccine is dependent on the presence of DNA vaccine in the nucleus, and (2) the amount of actual protein synthesized in a DNA vaccine and effectiveness of the protein being presented to immune system as an antigen following DNA vaccination vary significantly (See last paragraph, left column, page 389, Belakova et al., DNA vaccines: are they still just a powerful tool for the future? *Arch Immunol Ther Exp (Warsz).* 55(6):387-98, 2007). Furthermore, Belakova et al. states that different routes of administration lead to marked

different levels of protein expression as well as different levels of intensity and quality (Th1, Th2, antibody) of the immune response (See first paragraph, page 389, Belakova et al., 2007).

Directly related to instant application, with regard to the approach to enhance an immune response by the expression of a fusion protein, the status of art indicates the effect of fusion protein in eliciting an enhanced immune response for prevention of infection by a pathogen is unpredictable, because multiple factors/variations need to be considered. In this regard, Belakova et al. teaches heterologous antigen may play a role in modulating the immune response, the role may depend upon the nature of the antigen and/or the model system used (See bridging paragraph pages 393-394, Belakova et al., 2007), and the poor immune response to the majority of clinically tested DNA vaccines (See pages 394-395, Belakova et al., 2007).

Consistent with the unpredictabilities of DNA vaccination in general taught by Belakova et al., **Hu** discusses specific DNA vaccination in non-human primates (NHP) model in AIDS vaccine research. Hu teaches that a multitude of vaccines and immunization approaches have been evaluated, including DNA vaccines, and depending on the particular vaccine and model used, varying degrees of protection have been achieved, including prevention of infection, reduction of viral load, and amelioration of disease. Although sophisticated methodologies have been developed to define the mechanisms of protective immunity, a clear road map for HIV vaccine development, including DNA vaccine, has yet to emerge (See abstract, Hu, Non-human primate models for AIDS vaccine research. *Curr Drug Targets Infect Disord.* 5(2):193-201, 2005). Therefore, whether a protective immunity against HIV infection can be elicited in an individual by a DNA vaccine is unpredictable.

With regard to DNA cancer vaccine, consistent with the unpredictabilities of DNA vaccination in general taught by Belakova et al., **Mittendorf et al.** discusses, for instance, the search for breast cancer vaccines. Mittendorf et al. indicates that most of experimental DNA vaccines for preventing breast cancer have either not moved beyond preclinical testing or have not shown a significant clinical response. Mittendorf et al. teaches that prophylactic vaccines typically target infectious agents, but the evidence for an infectious etiology for breast cancer is largely descriptive and difficult to interpret. Mittendorf et al. teaches a strategy for a preventive breast cancer vaccine is to target tumor-associated antigens, and ongoing clinical trials are utilizing this approach, with preliminary results that are encouraging (See abstract, Mittendorf et al., Breast cancer vaccines: promise for the future or pipe dream? *Cancer*, 110(8):1677-86, 2007). Therefore, at the time of filing of instant application as well as at present, whether a protective immunity against development of breast cancer can be elicited in an individual by a DNA vaccine remains unpredictable.

Consistent with the teachings of Belakova et al., Hu, and Mittendorf et al. discussed above, **Ulmer et al.** indicates that DNA vaccines have been widely used in efforts to develop vaccines against various pathogens as well as for cancer, autoimmune diseases and allergy. Ulmer et al. teaches DNA vaccines offer broad efficacy (particularly for their ability to generate both cellular and humoral immunity), ease of construction and manufacture and the potential for world-wide usage even in low-resource settings; however, despite their successful application in many preclinical disease models, their potency in human clinical trials has been insufficient to provide protective immunity (See abstract, Ulmer et al., Gene-based vaccines: recent technical and clinical advances. *Trends Mol Med.* 12(5):216-22, 2006).

In view of the state of the art, the unpredictability in the art, and the lack of specific guidance and working examples in the specification, one of skill in the art would have to perform undue experimentation to make and use the claimed invention commensurate in scope with the claims 21-23, 54, 61-63, 65, 72-74, and 76.

Applicant's arguments and Examiner's ***Response to Applicant's arguments***

(i) Applicant argues that the specification discloses immunization protocols that include the administration of nucleic acid sequences that encode a fusion protein consisting of an IgE-leader sequence and a non-IgE protein sequence. The data illustrate that T cells from HIV-1 infected patients can be expanded by administration of the nucleic acid constructs (Specification, page 47). The data illustrate that the expansion is antigen-specific (Specification, page 46-50). The data illustrate that IL-15 expression enhances antigen-specific immune responses by imparting memory of CD8+ T cells (Specification, page 55). Increasing the expression of immunomodulating proteins likely enhances the effects of cytokine on demonstrate that the nucleic acid constructs of the present invention express either immunogen or immunomodulating proteins at levels dramatically higher than nucleic acid constructs that encode protein without the IgE leader sequence. The higher expression was shown to increase antigen expression or immunomodulating protein expression in cells originating from different species (see Figure 12 and page 42). The same DNA constructs also enhance the immune response of mice when administered as compared to negative controls (Examples Section and Figures 15-16 with accompanying text) (See pages 9-10 of Applicant's remarks filed on 01/29/2009).

In response: It is noted that page 47 of specification discloses the following information relevant of claimed pharmaceutical composition/recombinant vaccine of claim 1: Intracellular staining for Interferon-γ of stimulated murine cells --- Mice were given two injections with either pCgag DNA or pCgag DNA plasmid plus pIL-15. One week later, splenocytes were harvested and cultured *in vitro* for five hours in media containing a p55 peptide cocktail (containing 122 15mers spanning HIV-I p55 with 1 1 aa overlaps) and BrefeldinA. After stimulation, cells were

stained extracellularly with10 anti-mouse CD3 and anti-mouse CD8 antibodies and then intracellularly with anti-mouse IFN-γ. Dot plots display responses from CD3+/CD8+ lymophocytes. IL-15 was assessed for its ability to augment T cell effector activation, in a synergistic manner, with T cell receptor stimulation.

Amended claim 1 reads as follows: An isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of: a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide that is from the same species as the non-IgE protein; and a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide, wherein the non-IgE protein is an immunomodulating protein selected from the group consisting of cytokines, chemokines, cellular death receptors, cellular adhesion molecules, cellular growth factors, cellular growth factor receptors, protein kinases and enzymes or functional fragment thereof.

It is noted that the limitation "a nucleic acid sequence selected from the group consisting of" clearly indicates that the limitation "a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide that is from the same species as the non-IgE protein" and the limitation "a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide, wherein the non-IgE protein is an immunomodulating protein selected from the group consisting of cytokines, chemokines, cellular death receptors, cellular adhesion molecules, cellular growth factors, cellular growth factor receptors, protein kinases and enzymes or functional fragment thereof" are two different species that can be selected from to be the claimed "isolated nucleic acid".

Claim 1 does not recite any immunogen encoded by the isolated nucleic acid, which includes pCgag DNA disclosed in page 47 of specification. It is worth noting that nucleic acid that encodes an immunogen is recited in claim 16 to further limit claim 1. As disclosed in the specification, IL-15 expression can enhance pCgag DNA generated T cell mediated immune response. However, there is no evidence that expression of cytokine itself does generate T cell mediated immune response, which is in fact generated by expression of pCgag DNA. Therefore,

the disclosure does not provide enabling support of claimed pharmaceutical composition/recombinant vaccine of claim 1. Furthermore, the disclosure in the specification fails to provide evidence that the presence of CD3+/CD8+ lymphocytes in murine cells does provide protective immunity for the mouse. In other words, there is no evidence that stimulated murine cells with higher CD3+/CD8+ lymphocyte count provide protective immunity of mouse from future HIV infection.

(ii) Applicant argues that the initiation of a clinical trial in connection with the *in vitro* and *in vivo* data submitted with the application provide one of ordinary skill in the art with sufficient guidance to make and use the claimed invention commensurate in scope with the claims as amended. Applicant argues that the evidence cited by the Office which allegedly cast doubt on the enablement of the invention fails to establish a *prima facie* case for lack of enablement of the claimed invention.

In response, as clearly documented in the scope of enablement rejection, consistent with the teachings of Belakova et al., Hu, and Mittendorf et al. discussed above, Ulmer et al. indicates that DNA vaccines have been widely used in efforts to develop vaccines against various pathogens as well as for cancer, autoimmune diseases and allergy. Nevertheless, Ulmer et al. teaches DNA vaccines offer broad efficacy (particularly for their ability to generate both cellular and humoral immunity), ease of construction and manufacture and the potential for world-wide usage even in low-resource settings; however, despite their successful application in many preclinical disease models, their potency in human clinical trials has been insufficient to provide protective immunity (See abstract, Ulmer et al., Gene-based vaccines: recent technical and clinical advances. *Trends Mol Med.* 12(5):216-22, 2006).

The Examiner has noted that Belakova et al. discusses critical factors affecting effectiveness of a DNA vaccine. These factors include (1) efficacious expression of protein DNA vaccine is dependent on the presence of DNA vaccine in the nucleus, and (2) the amount of actual protein synthesized in a DNA vaccine and effectiveness of the protein being presented to

immune system as an antigen following DNA vaccination vary significantly (See last paragraph, left column, page 389, Belakova et al., DNA vaccines: are they still just a powerful tool for the future? *Arch Immunol Ther Exp (Warsz).* 55(6):387-98, 2007) --- which Applicant cited on page 10 of remarks filed on 01/29/2009. Nevertheless, Belakova et al. clearly states that different routes of administration lead to marked different levels of protein expression as well as different levels of intensity and quality (Th1, Th2, antibody) of the immune response (See first paragraph, page 389, Belakova et al., 2007).

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 1, 14-17, 19, 21-23, 54-63, 65-74, and 76 remain rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by **Weiner et al.** (US 2002/0123099, A1, Publication date Sep. 5, 2002). Applicant's arguments filed 01/29/2009 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 9-11 of the office action mailed on 07/29/2008.

For clarity and completeness of this office action, the rejection for the reasons of record advanced on pages 9-11 of the office action mailed on 07/29/2008 is reiterated below, with revision addressing claim amendments filed on 01/29/2009.

Amended claim 1 reads as follows: An isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of: a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide that is from the same species as the non-IgE protein; and a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide, wherein the non-IgE protein is an immunomodulating protein selected from the group consisting of cytokines, chemokines, cellular death receptors, cellular adhesion molecules, cellular growth factors, cellular growth factor receptors, protein kinases and enzymes or functional fragment thereof.

Claim interpretation: It is noted that the limitation "a nucleic acid sequence selected from the group consisting of" clearly indicates that the limitation (i) "a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide that is from the same species as the non-IgE protein" and the limitation (ii) "a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide, wherein the non-IgE protein is an immunomodulating protein selected from the group consisting of cytokines, chemokines, cellular death receptors, cellular adhesion molecules, cellular growth factors, cellular growth factor receptors, protein kinases and enzymes or functional fragment thereof" are two different nucleic acids that can be selected from to be the claimed "isolated nucleic acid".

In other words, to anticipate claim 1, the art is required to discloses either the limitation (i) "a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide that is from the same species as the non-IgE protein" or the limitation (ii) "a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide, wherein the non-IgE protein is an immunomodulating protein selected from the group consisting of cytokines, chemokines, cellular

death receptors, cellular adhesion molecules, cellular growth factors, cellular growth factor receptors, protein kinases and enzymes or functional fragment thereof".

It has been noted that the two inventors listed in the prior art Weiner et al. 2002 (David B. Weiner and Joo-Sung Yang) are also listed as the inventors of the four inventors listed in the instant application.

Weiner et al. teaches a secretory IgE signal leader sequence was fused to WNVC protein, which is the West Nile Virus (WNV) wild type capsid (Cp) protein. (See Figure 1, paragraph [0010]). Weiner et al. teaches an injectable pharmaceutical composition, a DNA vaccine, comprising a nucleic acid molecule that encodes a secretory IgE signal leader sequence was fused to WNVC protein, and the pharmaceutical composition/DNA vaccine is a plasmid or a recombinant vaccinia or adenoviral vector (See abstract, , paragraphs [0010]-[0013], [0071] and [0072], Weiner et al., 2002). Weiner et al. teaches WNCP is a non-IgE, immuno-modulating protein/immunogen that can be used to immunize an individual (See paragraphs [0081]-[0082], claim 2, Weiner et al., 2002). These teachings by Weiner et al., 2002 read on claims 1, 14-17, 19, 21-23, 54-76.

In addition to West Nile Virus (WNV) wild type capsid (Cp) protein, Weiner et al. teaches the pharmaceutical composition comprises HIV-1 gag structural gene (See Example 4, Weiner et al., 2002), or nucleic acid encodes non-immunogenic therapeutic proteins including cytokines, growth factors, blood products, and enzymes (See paragraph [0010] and claim 47, Weiner et al., 2002). These teachings by Weiner et al., 2002 reads on claim 38.

Thus, Weiner et al. clearly anticipates claims 1, 14-17, 19, 21-23, 54-63, 65-74, and 76 of instant application.

Applicant's arguments and Examiner's ***Response to Applicant's arguments***

Applicant argues that claim 1 has been amended to recites: An isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of: a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide that is from the same species as the non-IgE protein; and a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide, ***wherein the non-IgE protein is an immunomodulating protein selected from the group consisting of cytokines, chemokines, cellular death receptors, cellular adhesion molecules, cellular growth factors, cellular growth factor receptors, protein kinases and enzymes or functional fragment thereof***.

In response, claim 1 as written does not require the presence of both a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide that is from the same species as the non-IgE protein; and a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide, wherein the non-IgE protein is an immunomodulating protein selected from the group consisting of cytokines, chemokines, cellular death receptors, cellular adhesion molecules, cellular growth factors, cellular growth factor receptors, protein kinases and enzymes or functional fragment thereof. More elaboration has been provided in the *claim interpretation* of maintained rejection.

5. Claims 1, 14, 16, 17, 19, 21, 22, 54-56, 58-62, 65-67, 69-73, 74 and 76 remain rejected under 35 U.S.C. 102(b) as being anticipated by **Yang et al.** (Yang et al., Induction of potent Th1-type immune responses from a novel DNA vaccine for West Nile virus New York isolate (WNV-NY1999). *J Infect Dis.* 184(7):809-16, 2001). Applicant's arguments filed 01/29/2009

have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 11-12 of the office action mailed on 07/29/2008.

For clarity and completeness of this office action, the rejection for the reasons of record advanced on pages 11-12 of the office action mailed on 07/29/2008 is reiterated below, with revision addressing claim amendments filed on 01/29/2009.

Amended claim 1 reads as follows: An isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of: a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide that is from the same species as the non-IgE protein; and a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide, wherein the non-IgE protein is an immunomodulating protein selected from the group consisting of cytokines, chemokines, cellular death receptors, cellular adhesion molecules, cellular growth factors, cellular growth factor receptors, protein kinases and enzymes or functional fragment thereof.

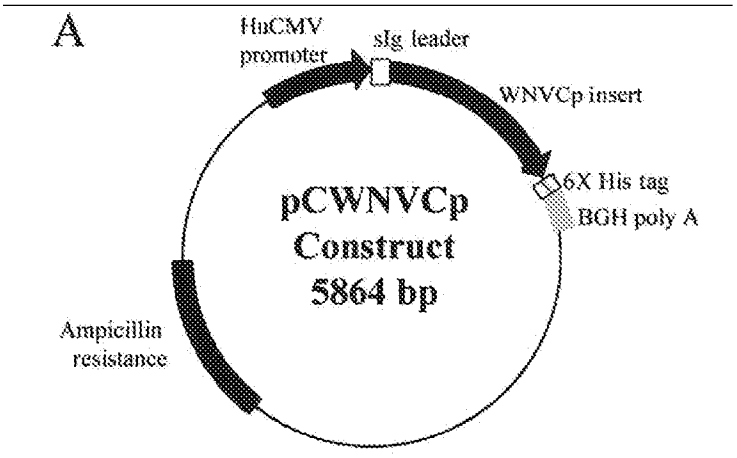
Claim interpretation: **(I)** It is noted that the limitation "a nucleic acid sequence selected from the group consisting of" clearly indicates that the limitation (i) "a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide that is from the same species as the non-IgE protein" and the limitation (ii) "a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide, wherein the non-IgE protein is an immunomodulating protein selected from the group consisting of cytokines, chemokines, cellular death receptors, cellular adhesion molecules, cellular growth factors, cellular growth factor receptors, protein kinases and enzymes or functional fragment thereof" are two different nucleic acids that can be selected from to be the claimed "isolated nucleic acid".

In other words, to anticipate claim 1, the art is required to discloses either the limitation (i) "a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide that is from the same species as the non-IgE protein" or the limitation (ii) "a nucleic acid sequence that encodes a fusion protein that consists of a non-

IgE protein sequences linked to an IgE signal peptide, wherein the non-IgE protein is an immunomodulating protein selected from the group consisting of cytokines, chemokines, cellular death receptors, cellular adhesion molecules, cellular growth factors, cellular growth factor receptors, protein kinases and enzymes or functional fragment thereof".

(II) In the absence any peptide sequence encoded by a nucleic acid sequence disclosed in specification and/or recited in the claims, the limitation "an IgE signal peptide" is given the broadest and reasonable interpretation to encompass any variations of signal peptide of an immunoglobulin E (IgE).

Yang et al. teaches a recombinant DNA vaccine, a plasmid construct, as a pharmaceutical composition comprises a nucleic acid sequence encoding the human immunoglobulin secretory leader signal (See sIg leader, indicated in Figure 1A, Yang et al., 2001, and the plasmid map provided below) fused West Nile Virus (WNV) capsid protein (Cp). Yang et al. teaches that antigen-specific humoral and cellular immune response were observed in mice injected intramuscularly with the DNA vaccine construct (See abstract, Figure 1, Yang et al., 2001).



Thus, Yang et al., 2001 clearly anticipates claims 1, 14, 16, 17, 19, 21, 22, 54-56, 58-62, 65-67, 69-73, 74 and 76 of instant application.

Applicant's arguments and Examiner's ***Response to Applicant's arguments*** are the same as documented in the maintained rejection of claims 1, 14-17, 19, 21-23, 54-63, 65-74, and 76 rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Weiner et al. (US 2002/0123099, A1, Publication date Sep. 5, 2002).

6. Claims 1, 14, 16, 17, 19, 21, 22, 54-56, 58-62, 65-67, 69-73, 74 and 76 remain rejected under 35 U.S.C. 102(b) as being anticipated by Yang et al. (Yang et al., Induction of inflammation by West Nile virus capsid through the caspase-9 apoptotic pathway. *Emerg Infect Dis*. 8(12):1379-84, 2002). Applicant's arguments filed 01/29/2009 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 12-14 of the office action mailed on 07/29/2008.

For clarity and completeness of this office action, the rejection for the reasons of record advanced on pages 12-14 of the office action mailed on 07/29/2008 is reiterated below, with revision addressing claim amendments filed on 01/29/2009.

Amended claim 1 reads as follows: An isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of: a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide that is from the same species as the non-IgE protein; and a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide, wherein the non-IgE protein is an immunomodulating protein selected from the group consisting of cytokines, chemokines, cellular death receptors, cellular adhesion molecules, cellular growth factors, cellular growth factor receptors, protein kinases and enzymes or functional fragment thereof.

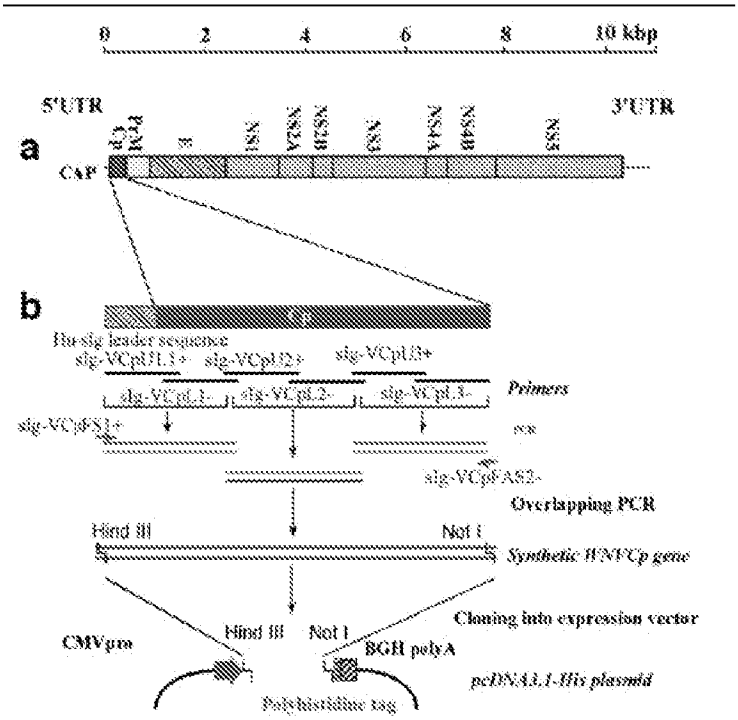
Claim interpretation: **(I)** It is noted that the limitation "a nucleic acid sequence selected from the group consisting of" clearly indicates that the limitation (i) "a nucleic acid sequence

that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide that is from the same species as the non-IgE protein" and the limitation (ii) "a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide, wherein the non-IgE protein is an immunomodulating protein selected from the group consisting of cytokines, chemokines, cellular death receptors, cellular adhesion molecules, cellular growth factors, cellular growth factor receptors, protein kinases and enzymes or functional fragment thereof" are two different species that can be selected from to be the claimed "isolated nucleic acid".

In other words, to anticipate claim 1, the art is required to discloses either the limitation (i) "a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide that is from the same species as the non-IgE protein" or the limitation (ii) "a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide, wherein the non-IgE protein is an immunomodulating protein selected from the group consisting of cytokines, chemokines, cellular death receptors, cellular adhesion molecules, cellular growth factors, cellular growth factor receptors, protein kinases and enzymes or functional fragment thereof".

(II) In the absence any peptide sequence encoded by a nucleic acid sequence disclosed in specification and/or recited in the claims, the limitation "an IgE signal peptide" is given the broadest and reasonable interpretation to encompass any variations of signal peptide of an immunoglobulin E (IgE).

Yang et al. teaches a recombinant DNA vaccine, a plasmid construct, as a pharmaceutical composition comprises a nucleic acid sequence encoding the human immunoglobulin secretory leader signal (See abstract, Hu-sIg leader indicated in Figure 1b, Yang et al., 2002, and the plasmid map provided below) fused West Nile Virus (WNV) capsid protein (Cp).



Yang et al. teaches that induction of inflammation mediated by T-cell activation in mice directly injected with the DNA vaccine construct (See right column, page 1381, Yang et al., 2002).

Thus, Yang et al., 2002 clearly anticipates claims 1, 14, 16, 17, 19, 21, 22, 54-56, 58-62, 65-67, 69-73, 74 and 76 of instant application.

Applicant's arguments and Examiner's ***Response to Applicant's arguments*** are the same as documented in the maintained rejection of claims 1, 14-17, 19, 21-23, 54-63, 65-74, and 76 rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Weiner et al. (US 2002/0123099, A1, Publication date Sep. 5, 2002).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1 and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Yang et al.** (Yang et al., Induction of potent Th1-type immune responses from a novel DNA vaccine for West Nile virus New York isolate (WNV-NY1999). *J Infect Dis.* 184(7):809-16, 2001) in view **Letvin et al.** (WO 99/16466, international publication date 04/08/1999). *This rejection is necessitated by claim amendments filed on 01/29/2009.*

Amended claim 1 reads as follows: An isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of: a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide that is from the same species as the non-IgE protein; and a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide, wherein the non-IgE protein is an immunomodulating protein selected from the group consisting of cytokines, chemokines, cellular death receptors, cellular adhesion molecules, cellular growth factors, cellular growth factor receptors, protein kinases and enzymes or functional fragment thereof.

Claim interpretation: **(I)** It is noted that the limitation "a nucleic acid sequence selected from the group consisting of" clearly indicates that the limitation (i) "a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide that is from the same species as the non-IgE protein" and the limitation (ii) "a nucleic

acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide, wherein the non-IgE protein is an immunomodulating protein selected from the group consisting of cytokines, chemokines, cellular death receptors, cellular adhesion molecules, cellular growth factors, cellular growth factor receptors, protein kinases and enzymes or functional fragment thereof" are two different species that can be selected from to be the claimed "isolated nucleic acid".

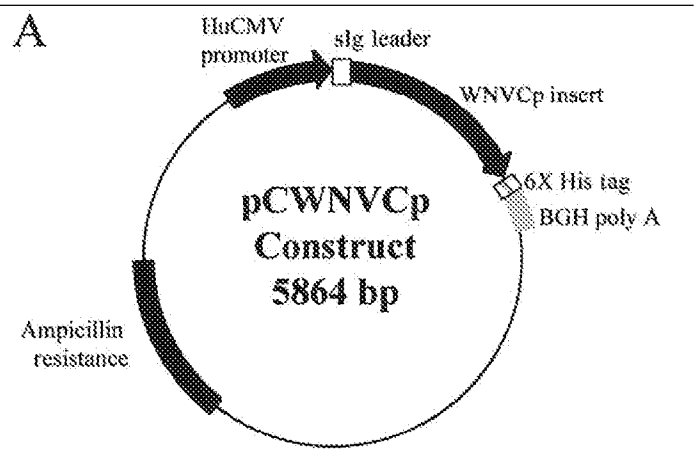
In other words, to anticipate claim 1, the art is required to discloses either the limitation (i) "a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide that is from the same species as the non-IgE protein" or the limitation (ii) "a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide, wherein the non-IgE protein is an immunomodulating protein selected from the group consisting of cytokines, chemokines, cellular death receptors, cellular adhesion molecules, cellular growth factors, cellular growth factor receptors, protein kinases and enzymes or functional fragment thereof".

Claim 77 is directed to IL-15 as an immunomodulating protein as Applicant elected IL-15 as the species for prosecution in the reply filed on 11/04/2009.

(II) In the absence any peptide sequence encoded by a nucleic acid sequence disclosed in specification and/or recited in the claims, the limitation "an IgE signal peptide" is given the broadest and reasonable interpretation to encompass any variations of signal peptide of an immunoglobulin E (IgE).

Yang et al. teaches a recombinant DNA vaccine, a plasmid construct, as a pharmaceutical composition comprises a nucleic acid sequence encoding the human immunoglobulin secretory leader signal (See sIg leader, indicated in Figure 1A, Yang et al., 2001, and the plasmid map provided below) fused West Nile Virus (WNV) capsid protein (Cp). Yang et al. teaches that

antigen-specific humoral and cellular immune response were observed in mice injected intramuscularly with the DNA vaccine construct (See abstract, Figure 1, Yang et al., 2001).



Yang et al. does not explicitly teach the limitation directing to the immunomodulating protein recited in claim 1 being IL-15 as recited in claim 77.

Letvin et al. (WO 99/16466) teaches the use of plasmid-expressed cytokines as a strategy for amplifying immune responses elicited by plasmid DNA vaccines and the cytokine may be e.g. IL-2, GM-CSF, IL-4, IL-6, IL-7, IL-13, IL-10, IL-12, **IL-15**, TNF-alpha or IFN-gamma (See for instance, page 11, lines 14-18, Letvin et al., 1999).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Yang et al. regarding a recombinant DNA vaccine, a plasmid construct, as a pharmaceutical composition comprises a nucleic acid sequence encoding the human immunoglobulin secretory leader signal (See sIg leader, indicated in Figure 1A, Yang et al., 2001, and the plasmid map provided below) fused West Nile Virus (WNV) capsid protein (Cp), with the teachings of Letvin et al. regarding the use of plasmid-

expressed cytokine IL-15 as a strategy for amplifying immune responses elicited by plasmid DNA vaccines, to arrive at claim 77 of instant application by substitution of WNVCp encoding sequences taught by Yang et al. with IL-15 coding sequence and fused to sIg leader in the context of the plasmid taught by either Yang et al. (2001) or Letvin et al. (1999).

One having ordinary skill in the art would have been motivated to combine the teachings of Yang et al. and Letvin et al. because Letvin et al. specifically teaches the expression of cytokines, including IL-15 and IL-2, as a strategy for amplifying immune responses elicited by plasmid DNA vaccines.

There would have been a reasonable expectation of success given (i) successful demonstration of the induction of potent Th1-type immune responses from a novel DNA vaccine for West Nile virus New York isolate (WNV-NY1999) and release of various cytokines by T-cells of immunized mice, by the teachings Yang et al. (See Figure 3, Yang et al., 2001), and (ii) successful demonstration of IL-2/Ig fusion protein in enhancement of antigp120 immune response elicited by pV1-gp120, by the teachings of Letvin et al. (See Example 8, pages 26-29).

Thus, the claimed invention as a whole was clearly *prima facie* obvious

The Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.* that forecloses the argument that a **specific** teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf). The Examiner notes that in

the instant case, even in the absence of recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.,* the suggestion and motivation to combine Yang et al. (2001) and Letvin et al. (1999) has been clearly set forth above in this office action.

Conclusion

8. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Patent Examiner
Art Unit 1632